Subthalamic deep brain stimulation versus best medical therapy for l-dopa responsive pain in Parkinson's disease

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Abstract: Pain is a frequently observed non-motor symptom of patients with Parkinson's disease. In some patients, Parkinson's-related pain responds to dopaminergic treatment. In the present study, we aimed to elucidate whether subthalamic deep brain stimulation has a similar beneficial effect on pain in Parkinson's disease, and whether this effect can be predicted by a pre-operative l-dopa challenge test assessing pain severity. We prospectively analyzed 14 consecutive Parkinson's patients with severe pain who underwent subthalamic deep brain stimulation. In 8 of these patients, pain severity decreased markedly with high doses of l-dopa, irrespective of the type and localization of the pain symptoms. In these patients, subthalamic deep brain stimulation provided an even higher reduction of pain severity than did dopaminergic treatment, and the majority of this group was pain-free after surgery. This effect lasted for up to 41 months. In the remaining 6 patients, pain was not improved by dopaminergic treatment nor by deep brain stimulation. Thus, we conclude that pain relief following subthalamic deep brain stimulation is superior to that following dopaminergic treatment, and that the response of pain symptoms to deep brain stimulation can be predicted by l-dopa challenge tests assessing pain severity. This diagnostic procedure could contribute to the decision on whether or not a Parkinson's patient with severe pain should undergo deep brain stimulation for potential pain relief.

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Subthalamic deep brain stimulation versus best medical therapy for L-dopa responsive pain in Parkinson's disease

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Abstract

Pain is a frequently observed non-motor symptom of patients with Parkinson's disease, but only in some patients, Parkinson-related pain responds to dopaminergic treatment. With the present study, we aimed at elucidating whether subthalamic deep brain stimulation has a similar beneficial effect on pain in Parkinson's disease, and whether this effect can be predicted by a pre-operative L-dopa challenge test assessing pain severity. We prospectively analyzed 14 consecutive Parkinson patients with severe pain who underwent subthalamic deep brain stimulation. In 8 of these patients, pain severity decreased markedly with high doses of L-dopa, irrespective of the type and localization of the pain symptoms. In these patients, subthalamic deep brain stimulation provided an even higher reduction of pain severity as compared to dopaminergic treatment, and the majority of this group was pain-free after surgery. This effect lasted up to 41 months. In the remaining 6 patients, pain improved neither by dopaminergic treatment nor by deep brain stimulation. Thus, we conclude that pain relief following subthalamic deep brain stimulation is superior to dopaminergic treatment, and that the response of pain symptoms to deep brain stimulation can be predicted by L-dopa challenge tests assessing pain severity. This diagnostic procedure might contribute to the decision on whether or not a Parkinson patient with severe pain will benefit from deep brain stimulation.

Introduction

Pain is a frequently observed and often burdensome non-motor symptom in Parkinson's disease (PD). Pain management is therefore an important concern in the treatment of PD patients. In some patients, pain fluctuates in parallel to motor symptoms and responds well to dopaminergic treatment [3]. Recently, pain types in PD were classified as follows: musculoskeletal, dystonic, neuropathic/radicular, primary/central, and akathisia-related [3,5]. Recent studies with follow-up times up to 24 months revealed that deep brain stimulation (DBS) in the subthalamic nucleus (STN) improves pain in PD [4,6,7,8]. So far, however, it remains unclear whether or not pain responsiveness to L-dopa is an appropriate predictor for surgical outcome regarding pain relief, and whether dopaminergic medication and DBS in the STN are equally efficacious for the treatment of PD-related pain. To gain further insights into these questions, we prospectively examined the surgical outcome of 8 PD patients who suffered from severe L-dopa responsive pain, and of 6 PD patients in whom severe pain was not ameliorated by L-dopa.

Methods

We selected all consecutive PD patients who underwent STN-DBS in our movement disorders center and suffered from severe, chronic (present for more than 6 months) and persistent (daily) pain, irrespective of its type or localization. Pain was evaluated during a standardized structured interview on motor and non-motor symptoms of PD, and classified according to its phenomenology along previous recommendations [3,5]. Of 46 operated PD patients since 2009, we identified 14 patients who suffered from severe pain, which was defined as an intensity of pain ≥ 7 as assessed with an ordinal scale ranging from 0 to 10 (0=absent, 10=maximal pain). These patients suffered from different types of pain (Table 1). DBS was performed because of PD-associated motor fluctuations that were not adequately

controlled with oral dopaminergic medication. This study was approved by the local ethical committee.

Before STN-DBS, all patients were asked whether pain was worse during OFF conditions, and improved on dopaminergic medication. To measure the response of PD-related pain to dopaminergic treatment, we performed an L-dopa challenge test in all patients 2-4 months before DBS. This test was performed as described before, and all dopaminergic drugs and analgesics were discontinued prior to this examination [4]. Immediately prior to L-dopa intake, we assessed motor symptoms with the Unified Parkinson's Disease Rating Scale (UPDRS) part III. Simultaneously, the intensity of pain was scored according to the ordinal pain scale from 0 to 10. Sixty and ninety minutes after L-dopa intake, we performed the same tests again, and we assessed the response to L-dopa as compared to baseline. Significant pain relief was defined as an improvement of at least 50% on the ordinal scale. After STN-DBS and off analgesics, we reassessed motor symptoms and pain in the same way and compared the outcome with best medical response in the L-dopa challenge tests.

For the comparison of related non-parametric measures, we used the Wilcoxon signed-rank test. We applied McNemar's test, a non-parametric method, to 2 × 2 contingency tables with a dichotomous trait, with matched pairs of subjects (nominal data: "significant improvement" versus "no significant improvement").

Results

Table 1 gives an overview on pre- and postoperative findings. Eight patients (1-8) suffered from severe pain which was significantly improved on L-dopa, and 6 patients (9-14) had concomitant pain which was not L-dopa-responsive in the pre-operative L-dopa challenge tests (improvement <50%). All patients took analgesics on a regular basis. Patient 2 suffered from severe neck pain without radicular deficits, but the neurosurgical indication for a ventral corpectomy and fusion was given because of pain severity and kyphotic dual level

spondylosis. However, because of massive dyskinesia and to optimize postoperative stabilization, it was decided to postpone the cervical operation until optimal post-DBS motor control was achieved. In the third and the fourth patient with exacerbating abdominal pain, examinations of the gastrointestinal system and the heart were normal. Patients 5, 7 and 8 reported that motor fluctuations and pain were not necessarily emerging simultaneously, but patients 1-4 and 6 reported that pain was worse off dopaminergic medication. Patients 9, 10 and 13 stated that pain was not fluctuating with motor symptoms, and patients 11, 12 and 14 were not sure whether the pain was better on dopaminergic medication or not.

After STN DBS, the first 8 patients revealed a >50% improvement of pain as compared to the OFF condition, but the pain in the other 6 patients improved less than 50% (McNemar test: $p<0.001$). As a most striking example, patient 5 suffered from L-dopa responsive pain in different body regions – after DBS, pain was improved in all affected regions. The first 8 patients discontinued analgesics, whereas the others did not. Six patients of the L-dopa-responsive group were completely pain-free after surgery (75%). In all of the 8 patients, pain relief by STN DBS was superior to L-dopa ($p=0.007$). However, pain remained unchanged in the 6 patients in whom pain was L-dopa-unresponsive ($p=0.7$). No patient complained of novel pain after DBS.

In all 8 patients with significant improvement of pain with DBS, pain responded within seconds to few minutes after an increase of voltage. We could not find specific DBS settings that were more likely to produce pain remission: we observed pain relief in patients with either monopolar or bipolar stimulation, and irrespective of the localization of electrode poles. In general, however, pain relief was best when motor symptoms were best controlled, and higher voltage was associated with better pain control.

UPDRS III scores improved in all patients after STN-DBS, and dyskinesia remitted. The follow-up intervals ranged from 3 to 41 months. Six patients regarded pain relief as the major improvement following DBS. In patient 2, cervical surgery was cancelled.

Discussion

This observational and preliminary study shows in agreement with previous studies that STN-DBS can produce complete remission of severe PD-related pain in a sub-group of PD patients. Furthermore, this selective response to surgery may be predicted pre-operatively by L-dopa challenge tests assessing pain severity: Pain with significant response to L-dopa was improved by STN-DBS. In addition, the comparison with L-dopa challenge tests suggests that high-dose L-dopa is inferior to STN-DBS for the treatment of PD-related pain. Regarding phenomenology, the different types of pain in our patients included musculoskeletal, primary, dystonic, and neuropathic pain, and all responded equally to DBS. This is in line with a short-term, randomized, cross-over study in 16 patients, where it has been suggested that STN-DBS raises pain thresholds in PD patients with pain and restored better functioning of the lateral discriminative pain system, i.e. the somatosensory cortices and posterior insula [2]. Similarly in a study of sensory detection and pain thresholds in 25 PD patients, an increased sensitivity to innocuous thermal stimuli but a reduced sensitivity to mechanical or thermal pain was found, and the authors concluded that STN-DBS contributes to pain relief by modulating small fiber-mediated sensations [1]. In agreement with these studies, the finding of complete alleviation of pain with STN-DBS in our patients suggests that pain was of central origin in all DBS-responsive patients, i.e. a direct consequence of the neurodegenerative disease itself rather than the result of rigidity, dystonia, peripheral neuropathy, or a musculoskeletal cause.

This study has limitations. First, pain assessment with an ordinal scale might not be sufficient, and a visual analogue scale might have been more appropriate. We decided to work with the ordinal scale, because the visual analogue scale was sometimes difficult to interpret in patients with severe tremor. Second, this study was open-label and un-blinded, and therefore a placebo effect cannot be ruled out. However, our patients showed subtle reactions to changes

in the setting and configuration of DBS, i.e. lowering amplitudes and changes of electrode poles increased pain even if patients were not aware of the change in stimulation parameters. Furthermore, a placebo effect might apply for the response to dopaminergic medication as well, but DBS was even more efficacious and often even led to complete pain relief. Third, the number of patients was low and did not allow for a thorough analysis of best DBS configuration and stimulation parameters (e.g. in respect to mode and exact localization of stimulation for best response to pain). Facing these limitations, further studies will be needed for a more thorough investigation.

In summary, we found that pain relief following STN-DBS surgery may be predicted by L-dopa challenge tests assessing pain severity off- and on-medication whereas assessment of the association between dopaminergic treatment and pain relief by history alone appears neither sensitive nor specific enough. Furthermore, our findings suggest that high-dose L-dopa is inferior to subthalamic deep brain stimulation for the treatment of Parkinson-related pain. Thus, pain relief in L-dopa challenge tests might be an additional clinical finding which should be considered in the decision-finding on whether DBS is indicated or not in a PD patient with severe pain. Finally, one of our patients reminded us to install optimal treatment of PD before initiating invasive procedures to treat concomitant pain, even if the phenomenological type of pain and additional examinations suggest another cause than PD itself.

Synopsis

Subthalamic deep brain stimulation is superior to best medication for improvement of Parkinson-related pain. This treatment effect can be predicted by preoperative L-dopa challenge tests.

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Contributorship statement:

Oguzkan Sueruecue: Performed DBS operation, wrote first draft of the manuscript.

Heide Baumann-Vogel: Performed electrophysiological testing during DBS, performed statistical analyses, assessed follow-up data on patients, helped with manuscript writing.

Lukas Imbach: Performed electrophysiological testing during DBS, helped with statistical analyses, assessed follow-up data on patients, helped with manuscript writing.

Mechtild Uhl: performed L-dopa challenge tests, helped with manuscript writing.

Christian Baumann: conceptualized the current study, helped with manuscript writing and statistical analyses.

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Table 1.

Demographic data, motor impairment and pain severity in 14 consecutive patients with Parkinson's disease, before and after subthalamic deep brain stimulation (STN-DBS). Motor impairment was assessed with the motor subscale of the Unified Parkinson's Disease Rating Scale (UPDRS III, here UIII), pain severity (PS) was scored according to an ordinal scale ranging from 0 to 10 (0=absent, 10=maximal pain). Pain types refer to the phenomenology of pain, as classified by others [3,5]. Mus-skel: Musculoskeletal. Abdom/visc: abdominal/visceral. Pat: Patient. LD-ED: Daily Levodopa-equivalent dose in mg, according to [9]. PS off, PS on: Pain severity during L-dopa challenge tests, off and on medication. D.D.: disease duration in years at the time of STN-DBS. Δ PS-LD: improvement of pain severity by L-dopa, compared to OFF condition. Δ PS-DBS: improvement of pain severity by STN DBS, compared to OFF condition. P=WSoD: pain is the worst symptom of the disease, as reported by the patient. P≈DT (h): pain is associated with dopaminergic treatment, as assessed by history. I DBS-MPA: Interval between STN-DBS and motor/pain assessment (months).